ISSUES IN MEDICINE

Surprises of off-label drug use – where had all the Prostin gone?

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The off-label use of drugs is common, particularly in paediatrics, where many drugs have yet to undergo the rigorous scrutiny demanded by authorities such as the Medicines Control Council (MCC) and the US Food and Drug Administration (FDA) before registration.[1,2] Yet some drugs (e.g. paracetamol, salbutamol) are so commonplace in paediatric practice that it may come as a surprise that their use is indeed off-label in many circumstances. Problems may arise when an important drug in everyday (off-label) use is unexpectedly in short supply. An example is dinoprostone, marketed in South Africa as Prostin E2 by Pfizer South Africa (but curiously not listed on their website). Its registered use in South Africa is for induction of labour (as an oral 0.5 mg tablet), yet it is commonly used in South Africa for the emergency maintenance of ductal patency in newborn babies.

Dinoprostone

Dinoprostone is a naturally occurring prostaglandin E_2 that binds and activates the PGE_2 receptor. It is often used as an emergency treatment to maintain the patency of the ductus arteriosus (PDA) in neonates with duct-dependent lesions such as certain forms of cyanotic congenital heart disease (e.g. pulmonary atresia or transposition of the great arteries) and interruption or coarctation of the aorta. The birth incidence of these rapidly life-threatening lesions is 1.0 - 1.8/1 000[3] and administration of dinoprostone is life-saving, 'buying time' for the baby to be transferred to a referral centre for definitive establishment of pulmonary or aortic blood flow by systemic-to-pulmonary shunt or arch repair, respectively. Without maintenance of ductal patency, duct-dependent babies rapidly become critically ill and die.

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Dinoprostone is also used for the longer-term maintenance of ductal patency in low-birth-weight infants with duct-dependent pulmonary circulations but branch pulmonary arteries that are too small for immediate surgical placement of a systemic-to-pulmonary artery shunt.[4]

For these applications, dinoprostone is usually administered as an oral medication. The 0.5 mg tablet is crushed and mixed with water and 0.125 mg aliquots (¼ tablet) are given to the infant by nasogastric tube every 30 - 60 minutes.[4] The side-effects are minimal, but include a small increase in body temperature (generally to less than 37.5°C) and loose stools. This simple method of administration is easily achievable by peripheral hospitals and delivery units, enabling rapid establishment of stable ductal patency before transfer to a tertiary referral centre.

An alternative, intravenous PGE_1 (alprostadil, Prostin VR), requires the placement of secure intravenous access for continuous infusion of alprostadil and close monitoring of respiratory effort. Intravenous PGE_1 frequently causes apnoea requiring intubation and ventilation for safe transfer. Peripheral hospitals and delivery units are often not capable of such interventions and do not stock intravenous PGE_1. There are no alternatives to maintain ductal patency.

The whistle-blower case

In January 2009 we received a call from a paediatrician at a regional hospital. A small infant with pulmonary atresia, dependent on a PDA for flow to his pulmonary arteries, required time to grow to sufficient size to enable the placement of a modified Blalock-Taussig shunt. After assessment at Red Cross War Memorial Children's Hospital he had been returned to the regional hospital for growth, receiving a quarter Prostin E2 tablet half-hourly for maintenance of his PDA. The hospital was about to run out of Prostin E2 and was unable to replenish the supply from local clinics or hospitals, since these had all also run out. No stocks were available from local suppliers. The baby was transferred back to Red Cross Hospital on intravenous alprostadil, and required early placement of a systemic-to-pulmonary artery shunt. The procedure was complicated by early shunt stenosis and re-operation was required for shunt revision, which could have been avoided had he been allowed to grow until the vessels were larger, lessening the risk of shunt thrombosis.

Where had all the Prostin gone?

Unbeknown to South African paediatric cardiologists and most pharmacists nationally, stocks of Prostin E2 had become critically depleted. Pfizer is said to have redesigned the packaging of Prostin E2, and stocks became depleted while awaiting re-registration with the Medicines Control Council.

Why did Pfizer fail to inform paediatric cardiologists and pharmacists of an imminent and foreseeable shortage? Apparently Pfizer representatives had informed obstetric/gynaecological practitioners, but according to their spokesperson they were 'not allowed' to discuss an off-label drug with paediatric cardiologists, despite the fact that Prostin E2 is the only oral dinoprostone available in South Africa and has been in use as outlined for many years. A rapid survey of all paediatric cardiac referral centres in South Africa revealed that this was a national problem in both the public and private health sectors. At the same time, Pfizer could not tell us with certainty when supplies would be resumed.

To their credit, when the potential impending crisis in congenital cardiac care was brought to Pfizer's attention in mid-January 2009, they expedited the delivery of fresh stocks to suppliers, and by Monday 26 January the supply of Prostin E2 had resumed nationwide. Pfizer assured us that there was sufficient stock 'for two years' and that future supplies would be 'uninterrupted', but unfortunately were not prepared to give these assurances in writing.

So ended a brief yet worrying period during which we could not ensure the safe transfer of neonates with duct-dependent congenital cardiac lesions and were having to start making difficult management decisions with regard to timing of their cardiac surgery. Nevertheless, it remains of concern that the supply of essential and life-saving drugs can be prone to sudden, unexpected interruptions; and perhaps more so that producers consider themselves legally constrained from disclosing imminent foreseeable drug supply interruptions if such drugs are used off-label. The reluctance of pharmaceutical companies to discuss issues pertinent to the use of off-label drugs – even urgent issues such as notification of interruption of supply – is grounds for much concern. It surprises us that medical practitioners working for this company are not prepared to inform colleagues – even 'off the record' – considering that Prostin is listed for paediatric use in the latest version of the essential drugs list for South Africa.[5]

The FDA becomes permissive

In the USA, the FDA's prohibition on pharmaceutical companies to inform medical practitioners of important changes in indications for off-label drugs has been judged in the US District Court of Columbia as unconstitutional, and the FDA's restrictive stance vigorously criticised. The judgment included the statement: 'In sum, the court finds that the restrictions in the Guidance Documents [of the FDA] are more extensive than necessary to serve the asserted government interest and that they unduly burden important speech.'[6] In essence, the district court therefore had found that the FDA had violated the First Amendment of the US Constitution. On appeal, the US Court of Appeals for the District of Columbia dismissed the finding of the district court pertaining to the unconstitutionality of the FDA's prohibitions on procedural grounds, since it 'was not ripe for decision', but noted that it 'certainly did not criticize the reasoning or conclusions of the district court'.[7]

Thereafter, the FDA reconsidered its role in the regulation of off-label drug use, suggesting 'a more permissive attitude toward the promotion of off-label uses of drugs'.[8] In its recently published 'Guidance for Industry' document[9] the FDA recognises 'that the public health can be served when health care professionals receive truthful and non-misleading scientific and medical information on unapproved uses of approved or cleared medical products'.

Conclusion

While US law is not necessarily applicable in South Africa, surely common sense demands that in the interests of public health, information of a life-threatening shortage of any drug,

Pfizer responds

Pfizer South Africa welcome this article, which seeks to inform and protect the interests of both patients and physicians, and thank *SAMJ* for the opportunity to clarify some of the points made for the benefit of readers.

Product shortages do occur from time to time for a variety of reasons. In the case of Prostin E2 we found ourselves in an unfortunate situation whereby our third party supplier ran out of stock. This was totally unexpected and, because they are a third party supplier, resulted in our having to follow a number of different logistical as well as regulatory processes.

Keeping patients and physicians informed and protecting their interests is of paramount importance to Pfizer South Africa, and we greatly appreciate feedback. We will incorporate De Decker *et al*.'s suggestions in our communications to ensure that all relevant health care professionals are promptly informed of such issues within the confines of the industry regulations, and assure readers of our commitment to providing uninterrupted access to our medicines for patients and physicians.

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even in off-label use, should be disseminated as widely as possible to relevant health professionals. This would allow clinicians and pharmacists to implement contingency plans and/or changes in management strategies in order to minimise potential loss of life or increased morbidity resulting from the shortage of the drug.

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